Transanal Endoscopic Operation (TEO) – Local experience in a South African Setting

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ABSTRACT

TITLE: **Transanal Endoscopic Operation (TEO) – Local experience in a South African Setting**

Background

It is well recognised that the adenoma-carcinoma sequence is the mechanism by which most colorectal malignancies arise. Dysplastic adenomas are the precursor lesions which can progress to adenocarcinoma and premalignant sessile villous adenomas represent a particular challenge. Their early detection and removal can prevent rectal cancer. Local excision of low rectal tumors has become increasingly popular as technical advancement has rendered it easier and more effective. Local tumour excision avoids the complications of radical surgery. Transanal endoscopic operation (TEO) and Transanal endoscopic microsurgery (TEM) are two equivalent techniques that have been widely adopted as the treatments of choice for large rectal adenomas and selected rectal cancers but has been under-employed in South Africa.

The aim of this study was to evaluate TEO (the simpler and more affordable platform of the two) by describing the dimensions and anatomical parameters of specimens resected and using this to investigate whether any of these are predictive of recurrence, and to evaluate the incidence of complications of this less radical technique.

Methods

In this single surgeon study, data was collected from pre-existing patient files (paper and electronic) during the first half of the time period and during the second half, was prospectively entered into a database. It includes all patients undergoing resection of benign and malignant rectal tumours by TEO at a private (Kingsbury Hospital) and public health institution (Groote Schuur Hospital) from January 2009 – May 2017. Electronic records, including operation notes, histology and radiology were reviewed.

Results

Data was collected from January 2009 to May 2017. 110 patients in this study of which 87 (79.1%) were benign. There were 11 (12%) recurrences in this group. In the malignant group, there were 5 (21%) recurrences. The median tumour length was 4.5cm (IQR 2.5) and median tumour area was 16cm^2 (IQR 20.11).

For benign lesions, there was a significant difference in recurrence in patients presenting with incontinence (χ^2 8.21, *p*-value<0.01, OR 16.7 (1.37-202.7)), lesions with involved surgical margins (χ^2 6.29 *p*-value 0.01, OR 6.75 (95% CI 1.02 - 35.7)) and circumferential tumours (χ^2 6.31 *p*-value 0.04, 6.5 (1.17-36.3)). The multinomial logistic regression model for benign lesions revealed that only incontinence and involved surgical margins were independent predictors of recurrence. Complications occurred in 21 (19.1%) patients with circumferential lesions, length of the tumour, and malignancy being predictive of complications.

Conclusion

This study constitutes the only report of TEO or TEM from a low- or middle-income country (LMIC). The results are in keeping with the published literature, demonstrating its safety and feasibility in a LMIC setting, which will reduce the need for expensive, highly morbid radical surgery for benign and malignant disease. The recommendation is for a wider introduction of TEO in South Africa and other LMIC countries with the provision of adequate training.

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CHAPTER 1

1. Literature Review

1.1. Introduction

Colorectal cancer is one of the leading causes of death in developed countries, with a mortality rate of 8% (608 per 100 000). In men, it is the 4th most common cause of death (mortality rate 7.6%; 320 deaths per 100 000), after lung cancer (mortality rate 22.5%, 951 deaths per 100 000), stomach cancer (mortality rate 11%, 464 deaths per 100 000) and prostate cancer (mortality rate 6.1%, 258 deaths per 100 000). In women, it is the 3rd most common cause of death (mortality rate of 8.6%; 288 deaths per 100 000), after breast cancer (mortality rate of 13.7%; 458 deaths per 100 000) and lung cancer (mortality rate of 12.8%; 427 deaths per 100 000).[1]

Worldwide, incidence rates vary in both sexes. It was found to be the third most common cancer in men with an incidence of 10% (663 new cases per 100 000), after lung cancer (incidence rate of 16.5%; 1095 per 100 000) and prostate cancer (incidence rate of 13.8%; 913 per 100 000 person years) and third most common cancer worldwide. It is the second most common cancer in women (incidence rate of 9.4%; 570 new cases per 100 000) after breast cancer.[1,2]

Overall, the rates in Australia/New Zealand and Western Europe were estimated to be the highest compared to those in South Central Asia and Africa (except Southern Africa) being the lowest.[1] A study, comparing the incidence rates of colorectal cancer from 1982-87 to 1998-2002, found that the rates increased for both males and females in 27 of the 51 registries reviewed. This increase appeared to be limited to developing or 'economically transitioning' countries (Czech Republic, Slovakia and Japan) and exceeded the incidence in well-established developed countries (United States, Canada and Australia). The factors which may have contributed to this variation in incidence are synonymous with those associated with economic development and include the difference in prevalence of risk factors for colorectal cancer (obesity, physical inactivity, smoking, heavy alcohol consumption, a diet high in red or processed meats, a diet low in fruits and vegetables) and the difference in screening practices.[3,4]

Most recent statistics reported by the American Cancer Society include 95 270 cases of colon cancer for 2016 and 39 220 rectal cancer cases.[5] A retrospective cohort study evaluating the incidence patterns of colorectal cancer in the United States from 1974-2013 revealed that incidence rates of colon cancer increased by 1% to 2.4% annually since the mid-1980's in adults age 20-39 years and by 0.5% to 1.3% since the mid-1990's in adults age 40-54 years. In adults aged 55 years and older, the incidence rates generally declined, suggesting a possible role for screening before the age of 50.[6] This can be expected in other HICs (high income countries) in the next few years.

There is a paucity of data for the incidence of colorectal cancer in Africa. Colorectal cancer incidence rates tripled in Algeria from 1986-89 to 1998-2002 but remained stable in Mali, Uganda and Zimbabwe.[3] An article detailing the Global Cancer Statistics showed that the lowest incidence rates are found in Africa when compared with Australia, New Zealand, Europe and North America. The highest rates in Africa were noted in Southern Africa (20.4 per 100 000 for males and 8.2 per 100 000 for females).[7] The mortality rate in Southern Africa was 2.4 per 100 000 in men and 1.4 per 100 000 in women compared with those in developed countries (166.2 per 100 000 in men and 153.9 per 100 000 in women).[1] Interestingly, the mortality-to-incidence rate ratio in Africa was high (0.89), where an MR:IR approaching one suggests limited survival, in comparison to North America (0.34).[3,4] Five-year survival rates are not available for Africa but those in America are high for early stage disease (74% for stage I, 65% for stage IIa and 52% for stage IIb) and decrease significantly for late stage disease (32% for stage IIc and 6% for stage IV).[4] This is also not known in South Africa since the only document reporting on colorectal cancer is more than a decade old.

Data from this National Cancer Registry detailed the incidence of histologically diagnosed cancer in South Africa from 1996-1997. It reported a total of 854 and 1047 new colorectal cancers in females in 1996 and 1997 respectively, which constituted 3.4% of all cancers in females. Similarly, a total of 894 and 1089 were diagnosed in males for the same periods, constituting 3.6% of all cancers in males. Colorectal cancer therefore was the third leading cancer in females and the fifth leading cancer in males.[8] However, this national registry is pathology-based, incorporating many state and private laboratories and could have resulted in under-reporting.

Adenoma-Carcinoma Sequence

It is well recognised that the adenoma-carcinoma sequence is the mechanism by which most colorectal malignancies arise. It is a series of molecular and genetic alterations which result in histopathological effects. These genetic changes accumulate over many years and include, the loss of the tumour suppressor gene, adenomatous polyposis coli (*APC*) and mutations in *KRAS*, *PIK3CA* and *p53*. Dysplastic adenomas are the precursor lesions which can progress to adenocarcinoma.[9,10] Early detection and removal can prevent rectal cancer.[11]

There is controversy regarding the best surgical approach for early stage rectal cancer. Radical surgery, which involves excision of the rectum with its lymphatic drainage, offers the best chance of cure, but at the cost of significant morbidity, mortality and cost. Local tumour excision avoids the complications of major pelvic surgery.[12] Transanal endoscopic operation (TEO), which equates to the technique of Transanal Endoscopic microsurgery (TEM) has been widely adopted as the treatment of choice for large rectal adenomas. However, this has received minimal exposure in South Africa with the exception of two centres in Cape Town.

1.2. History

The excision of low rectal lesions has evolved from the transanal approach using open retraction, to an endoscopic approach. This includes several platforms using a rigid fibreoptic scope: TEM, TEO, TAMIS (transanal minimally invasive surgery). A purely endoscopic approach is used for endoscopic mucosal resection and endoscopic submucosal dissection.[13]

Transanal endoscopic operation owes its' origin to TEM, transanal endoscopic microsurgery, a technique pioneered by the late Gerhard Buess in Germany the early 1980's. In collaboration with the Richard Wolff Company, he developed instruments to perform endoscopic surgery transanally to excise low and middle rectal adenomas and early cancers not amenable to colonoscopic or local resection. The TEM system consists of four parts: the insufflating unit (which includes pressure monitoring, suction irrigation and provides the carbon dioxide), a removable face plate with ports, a rectoscope and a stereoscope allowing for magnification. TEM is a very expensive, minimally invasive technique, requiring dedicated equipment and has a steep equipment learning curve, especially using

the insufflator which provides a stable pneumorectum, thus facilitating a magnified view of the intraluminal rectum.[12–15]

In 1991, Karl Storz developed a similar system for transanal surgery which is cheaper, simpler and less complicated. It consists of a rectoscope tube 4cm in diameter which allows the use of rectoscopes of varying lengths (7.5cm, 15cm, 20cm). Standard laparoscopic instruments and camera system can be used with this device. A standard laparoscopic insufflator is used.[14,16,17] Unlike TEO, the TEM system requires appropriate positioning of the patient to place the lesion at 6 o'clock in the operating field. This is not a requirement for the TEO device and represents a significant advantage over TEM.[13,18] Another difference between the two is the three-dimensional vision offered by the TEM endoscopic procedure compared with a two-dimensional high definition vision offered by TEO.[19]

The literature available for TEM ranges from retrospective reviews to randomised controlled trials and systematic reviews. However, the literature for TEO specifically is quite sparse. As a consequence, most of the data presented in this review has been acquired from research with TEM but these can rationally be extrapolated to TEO.

A prospective randomized clinical trial comparing the effectiveness of TEM with TEO showed that no technical or clinical statistically significant differences were observed between the results obtained with the two systems. There were no statistically significant differences between pre-operative (time taken to assemble equipment, surgical time, quality of pneumorectum) and post-operative variables (morbidity and mortality) or pathology results. TEO was favoured with respect to a shorter time taken to assemble the equipment, surgical suture time and total operative time but it was not statistically significant. TEM was found to be significantly more expensive than TEO.[19]

1.3. TEM compared with Transanal Excision

Transanal excision has been demonstrated to be adequate in premalignant lesions and in early stage rectal cancer of the mid- and lower rectum without poor prognostic features and imaging that demonstrates no lymph node involvement.[12] It is limited to tumours of less than 4cm in diameter located in the lower third of the rectum. Lesions in the middle and upper rectum are inaccessible with this

technique. Visualisation is often suboptimal resulting in inadequate and inaccurate oncological resection, higher rates of tumour fragmentation and higher recurrence rates.[13] A systematic review and meta-analysis comparing TEM and transanal excision for the removal of rectal lesions found that TEM was oncologically superior. While their postoperative complication rate was comparable (OR, 1.018; 95% CI, 0.658–1.575; *p*-0.937), TEM had a higher rate of negative resection margins (OR, 5.281; 95% CI, 3.201–8.712; $p < 0.001$) and a lower rate of specimen fragmentation (OR, 0.096; 95% CI, 0.044–0.209; $p < 0.001$) and lesion recurrence (OR, 0.248; 95% CI, 0.154–0.401; $p < 0.001$).[15]

A retrospective review comparing TEM and transanal excision found similar results: TEM had negative resection margins of 50% compared 88% after transanal excision. Specimen fragmentation rate (1.4% and 23.8% respectively) and recurrence rate was much lower (3.2% for negative margins and 7.7% for positive margins for TEM and 0% and 59.6% for transanal excision.)[20]

TEO was compared with transanal excision in a case-matched study with propensity score matching in an attempt to mitigate selection bias and increase the level of evidence of an observational non-randomised study. This retrospective review also showed that the while the complication rates in the two groups were similar (TEO: 8.3% versus transanal excision: 11.1%, *p*-value 0.39), TEO had a higher negative resection margin rate (95.8% versus 86.1%, *p*-value 0.039) and a better non-fragmented specimen rate (98.6% compared with 90.3%, *p*-value 0.029).[21]

1.4. TEM compared with Endoscopic Submucosal Dissection

Endoscopic submucosal dissection (ESD) is a technique which enables en bloc removal of epithelial lesions via endoscopic resection. It was initially described as a non-operative method to manage gastric neoplasia. With the evolution of techniques and equipment for ESD, the applications have expanded to included other parts of the gastrointestinal tract.[22,23] ESD was compared to TEM for large non-invasive rectal lesions in a systematic review and meta-analysis. While ESD was found to be safe and did not require general anaesthesia, TEM had a statistically significant higher rate of en bloc and R0 resection. The en bloc resection rate was 87.8% in the ESD series and 98.7% in the TEM series and the R0 resection rate was 74.6% and 88.5% respectively. The recurrence rate of

adenomas was 2.6% in the ESD series and 5.2% in the TEM series, but this could be accounted for by the much shorter follow-up period in the ESD series (6-12 months) compared with an average follow-up period of 58.9 months.[23]

1.5. TEM compared with Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) is an endoscopic procedure which removes gastrointestinal lesions in the plane of the middle to deep submucosal layer, rather than the mucosal plane used in a standard polypectomy. Similar to ESD, it provides en bloc resection specimens.[24] A retrospective review of patients undergoing TEM or EMR for rectal adenomas greater than 2cm found that EMR for large rectal adenomas often results in a piecemeal resection with a higher risk of recurrence requiring re-intervention. The authors investigated recurrence rates after a single intervention (early) and after permitting re-treatment for residual adenoma within 6 months (late). Early recurrence rates were 10.2% in TEM and 31% in EMR patients. And late recurrence rates were 9.6% and 13.8% respectively. Perioperative complication rates for TEM and EMR were 2% and 6% and the post-operative complication rates were 24% and 13%. The authors concluded that after a single intervention EMR was safer but less effective than TEM. If retreatment of a residual adenoma was included within 6 months, TEM and EMR were equally effective.[25]

The TREND Study, a randomised control trial comparing the clinical outcome and cost effectiveness of TEM and EMR for large rectal adenomas, was unable to demonstrate statistical non-inferiority of EMR with respect to recurrence rates. The recurrence rates were 15% and 11% for EMR and TEM respectively and complications occurred in 18% and 26%. EMR was found to be more cost-effective. A concerning finding was the high rate of unexpected malignancies. Thirteen percent of the large adenomas harboured invasive disease and were excluded from the analysis resulting in a limitation of intention-to-treat analysis as acknowledged by the authors.[26]

1.6. Indications

Historically, the indications for TEM included benign lesions and invasive lesions in patients who were evaluated as being high risk of morbidity and mortality after radical resection, namely, anterior resection or abdominal perineal resection (APR). They have now expanded to being an effective option in all rectal

tumours (adenomas, carcinoid, GISTs), including circumferential and proximal lesions, fistulous disease (high anorectal fistulas, rectourethral & rectovaginal fistulas), anastamotic strictures, correction of rectal prolapse and most pertinently, early stage rectal cancer.[12,23,27] The indications discussed below include: Benign, malignant, repeat TEM, salvage therapy and TEM and adjuvant therapy.

1.6.1. Benign

The most common indication for TEM is benign, sessile low or middle rectal adenomas which cannot be removed colonoscopically or by transanal excision.[13,18,28] A systematic review assessing the safety and efficacy of TEM in 3 comparative studies and 55 case series found that complication rates ranged from 3 – 7% and local recurrence was 6% compared with 22% in the transanal excision group (with a median local recurrence of 5% for TEM).[29]

TEM was initially indicated in mid-to low rectal adenomas defined as lesions of the extra-peritoneal rectum. There is an increased risk of peritoneal perforation following TEM in upper and anterolateral rectal tumours. In addition, it makes the maintenance of a stable pneumorectum difficult.[30] In a retrospective review assessing the efficacy of TEM for lesions located in the upper rectum, defined as more than 10cm from the anal verge, the subgroup of patients with benign lesions (74 adenomas with or without high grade dysplasia) the local recurrence rate was 5.1% at a median follow-up of 8.7 years. In this study, the rectal wall was perforated intra-operatively in 3 patients (3%). After primary repair of the defect, 1 patient leaked post-operatively, requiring a formal anterior resection and diverting ileostomy.[31] Khoury et al., concluded that TEM is feasible and may be safe in selected cases. In addition to expanding the indication for TEM to upper rectal tumours, its use has recently expanded to larger, circumferential adenomas.

There is no universally accepted definition of a large adenoma with some reporting lesions over 2cm as large, while others only included circumferential lesions. A systematic review and meta-analysis of endoscopic mucosal dissection (ESD) versus TEM for large (more than 2cm) non-invasive rectal lesions showed that TEM achieved a higher R0 resection rate (88.5% for TEM compared with 74.6% for ESD) but a higher recurrence rate (5.2% versus

2.6%).[23] The TREND study, investigating lesions larger than 3 cm, reported recurrence rates of 15% and 11% for EMR and TEM respectively. Complications occurred in 18% and 26%. This study failed to demonstrate non-inferiority of EMR.[26]

There were two retrospective reviews that defined lesions greater than 5cm. In a European study (n =33) investigating giant rectal adenomas treated by TEM, a local recurrence rate of 12% and complication rate of 39.4% was demonstrated. The recurrence in all four patients (12%) were located in the lower third of the rectum and managed by conventional transanal excision.[32] Similarly, another study describing a series of 25 patients with rectal lesions greater than 5cm excised by TEM, had a local recurrence rate of 10.9% after a median follow-up of 2 years.[33] Lastly, there is only one retrospective review that described the use of TEM for giant circumferential lesions (n=17). Four patients required endoscopic balloon dilatation for anal stenosis, one patient had post-operative bleeding requiring a second TEM and no patients developed faecal incontinence or urinary or sexual dysfunction.[34]

1.6.2. Malignant

The increase in the incidence of early rectal cancer can be attributed to the widespread introduction of screening programs.[14,35] With the advancement in diagnostic, staging and treatment modalities, there is an increasing trend towards rectal-sparing treatment options including TEM and chemoradiotherapy.[35]

The current standard of care for the treatment of rectal cancer, when sphincter preservation is possible, is TME (total mesorectal excision). Despite the low recurrence and favourable long-term survival rates, it is associated with high rates of mortality and morbidity, including postoperative complications such as bleeding, anastomotic dehiscence, temporary or definitive colostomy and sexual or urinary dysfunction. TEM provides a more elegant transanal solution with minimal morbidity but does not provide for lymph node sampling.[14,18,35]

Early Rectal Cancer (T1)

Previously, TEM was indicated for low risk, early cancers (pT1 N0) defined as tumours with favourable prognostic factors, that is, size less than 4 cm, well-differentiated histology and an absence of vascular, lymphatic and perineural

invasion. The adherence to these criteria resulted in similar recurrence rates in TEM and radical resection but with lower morbidity and mortality.[36]

In a prospective study aimed to determine the prognostic factors for recurrences and the need for reoperation in patients with pT1 carcinoma resected by TEM, the recurrence rates and 10-year cancer-free survival were reviewed. The low risk group (R0 resection) had a recurrence rate of 6% and those in the high-risk group (unfavourable histology, R1, Rx, R1 < 1mm) had a recurrence rate of 39%. This high recurrence rate was reduced to 6% by re-operation. Furthermore, the 10-year cancer-free survival in the high-risk group was 93% after re-operation. In patients with low risk pT1 rectal carcinomas, TEM can provide adequate oncological treatment.[37]

In a randomized trial comparing TEM and anterior resection for early rectal carcinomas (T1), there were significant differences in length of hospital stay, blood loss, operating time and opiate analgesia, all favouring TEM. While there was a difference between local recurrence and 5-year survival rates, it was not significant. This study proved comparable rates of recurrence in TEM to the gold standard and showed a lower morbidity.[38]

An evidenced-based review of the current indications, controversies and future perspectives of TEM in the management of rectal cancer, which includes 72 studies, found that TEM is the ideal procedure for the local excision of selected early rectal cancers, offering a lower morbidity and mortality with no impairment of anorectal function and quality of life. The long-term survival following TEM for low risk T1 cancers is similar to that achieved after TME. In addition, the review showed that there is a role for full-thickness TEM in patients with intra-peritoneal rectal cancers with no increase in morbidity or mortality.[35]

Risk factors for recurrence after TEM for rectal neoplasms were evaluated in a retrospective study. The univariate analysis revealed that diameter, sm stage, pT stage, tumour grading, margin infiltration, and lymphovascular invasion were statistically significant. The multivariate analysis indicated sm stage, pT stage, and tumour grading as independent predictors of recurrence. Submucosal infiltration represented a significant risk factor for recurrences: 0% sm1, 16.7% sm2, and 30% sm3, with recurrence rates of 0% in pT1sm1 cancers and 22.7% in sm2-3 ($p < 0.05$).[39] Submucosal involvement also relates to nodal involvement.

In a review focussing on the inclusion criteria of early rectal cancer, nodal involvement in T1 cancer according to the grade of submucosal invasion was found to be 0-3.2% for sm1, 8-11% for sm2 and 12-25% for sm3.[40]

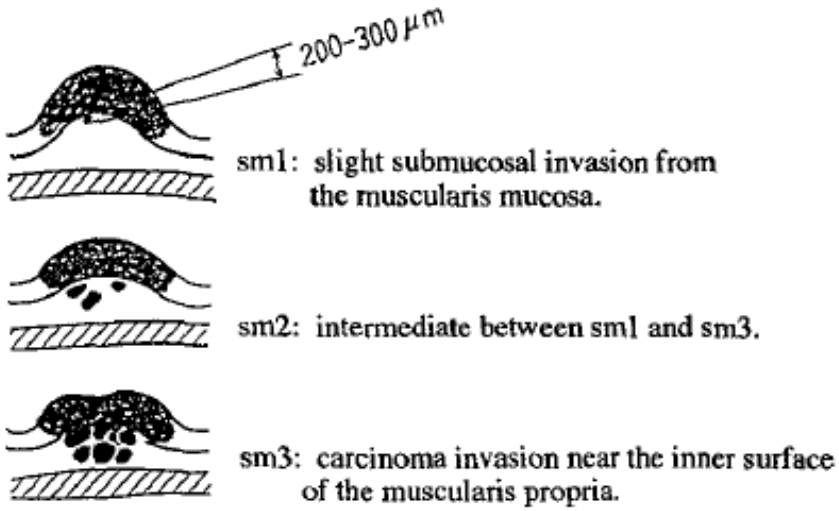

Figure 1: Kikuchi classification of level of invasion of early invasive cancer [41]

T2 and T3 Rectal Cancer

The indication for TEM has expanded. There is a concern regarding the adequacy and efficacy of TEM for T2 and T3 rectal cancer because of high recurrence rates and the lack of a lymphadenectomy.[18,35,38] The risk of lymph node involvement for T2 and T3 rectal adenocarcinomas is high. The stage of the primary tumour determines the risk of lymph node involvement, with nodal positivity being 10-13% in T1 tumours and 17-22% in T2 tumours.[42,43]

Tumour characteristics are also important in predicting lymph node metastases in rectal cancer.[15] A population-based study investigating the risk factors for lymph node metastases found that a T2-stage, poor differentiation and vascular infiltration were significant risk factors. The risk of lymph node metastases for T1 and T2 rectal cancers was 65% and 78% respectively when associated with poor differentiation and vascular infiltration. The analysis also indicated that high-risk T1 tumours had a greater probability of having lymph node metastases than low-risk T2 tumours suggesting that curative resection for low-risk T2 tumours is a possibility. Furthermore, the concept of local excision as a 'macro biopsy' with subsequent immediate radical resection in high risk cases was proposed.[44]

Another important factor is tumour location. A retrospective review for sessile T1 rectal cancer demonstrated that, in addition to lymphovascular invasion and sm3 depth of invasion, tumours located in the lower third of the rectum are at high risk of lymph node metastasis.[15,43]

Accurate pre-operative staging for rectal cancer is important when planning surgery, but despite advancements in imaging techniques, the pre-operative staging of nodal status is inadequate.[44] Magnetic resonance imaging (MRI), endorectal ultrasound (ERUS) and computed tomography (CT) are used for the pre-operative assessment of a patient being considered for TEM. While ERUS is able to differentiate between the layers of the rectal wall and thus determine the T-stage, and is the most accurate for early tumour invasion of the rectal wall when reported by experts, it is not readily available, is operator-dependent and has a limited depth of penetration to be used for nodal staging.[45,46] For MRI, the accuracy of T-staging ranges between 66% and 91% and N-staging between 65% and 88%.[47]

A few studies have found that there was no statistically significant difference in 5 year survival rates in patients with T2 lesions but there was an increased risk of local recurrence.[18] A prospective study, which sought to determine the value of local excision for T2 rectal carcinomas, prognostic factors and the need for re-operation (repeat TEM), found that of their 649 patients, 44 had a T2 lesion. An immediate re-operation was recommended but 24 patients declined further surgery or were not fit for surgery due to comorbidities. The local recurrence rates following local R0 resection of the low risk T2 tumours were 29%. Patients with unfavourable criteria, namely, involved resection margins (R1), a distance of tumour to the resection margin of less than 1mm (R<1mm), tumour fragmentation or an unclear resection margin (Rx), poor histological tumour grade (G3-4) and lymphovascular invasion, developed recurrences in 50%. But after salvage surgery, that is, immediate re-operation, the local recurrence was reduced to 7%. Thus an initial poor local resection result did not have an adverse oncological outcome.[48]

1.6.3. Repeat TEM for Benign and Malignant Disease

A retrospective review of patients who had a repeat TEM, for involved resection margins of locally excised cancer or benign local recurrence, demonstrated

favourable short-term outcomes similar to those following a primary TEM. There was no statistically significant difference between the mean operative times and intra- and post-operative complication rates. Furthermore, a repeat TEM did not impair anal sphincter function.[49] Similarly, a prospective study evaluated the safety and efficacy of repeat TEM after R1 endoscopic resection or local recurrence of early rectal cancer after operative endoscopy and found that a repeat TEM can be used as diagnostic procedure and a curative treatment modality before proceeding to a more invasive TME.[50]

1.6.4. TEM and Adjuvant Therapy for Malignant Lesions

TEM following Neoadjuvant Therapy

In a select group of patients with low rectal cancer, neoadjuvant therapy combined with TEM may be an alternative treatment option to TME. Neoadjuvant therapy may improve tumour resectability, allow for sphincter-preserving procedures and better local control of the disease.[35,51] A prospective randomised trial compared TEM and laparoscopic TME in patients with small, low rectal cancer following neoadjuvant chemoradiotherapy. The recurrence rates were similar in the two groups and there was no statistically significant difference in disease-free survival.[51] An evidence-based review of TEM in the management of rectal cancer, demonstrated that adequate oncological results could be achieved in highly selected T2 N0 rectal cancers but recommended that this be proposed in the setting of a clinical trial until the results are verified by more robust studies.[35]

Adjuvant Therapy following TEM

A meta-analysis of oncological outcomes after local excision of unfavourable pT1 and pT2 rectal cancer requiring adjuvant chemoradiotherapy or completion surgery found that the local recurrence rate was higher in patients with locally excised pT1/pT2 rectal cancer treated by chemoradiotherapy than in patients who had a completion TME. There were a number of limitations in this meta-analysis. The two groups were not directly comparable. Radiotherapy schedules were not identical among the cohorts and some patients received radiotherapy alone. The authors concluded that the standard of care after local excision or endoscopic resection of high-risk pT1 and pT2 rectal cancer remains a completion TME, but that in selected patients with intensive follow-up and early

salvage of recurrence, adjuvant therapy could be investigated as a less invasive treatment strategy.[52]

1.7. Rationale

TEM or TEO is a well-established technique which is indicated as a definitive treatment for benign adenomas and pT1sm1 carcinomas. T1 sm2-3 and T2 lesions should only be included in prospective trials after having been thoroughly staged pre-operatively. With advancing technology and surgical expertise, the indications are expanding. In South Africa, there is no data regarding the experience of the outcomes of TEO for benign rectal adenomas and early rectal cancer. This research will assist in identifying whether TEO is applicable to low- and middle-income countries (LMIC) for less invasive management of benign adenomas and early rectal cancer.

1.8. Aim

The aim of this study was to evaluate TEO (the simpler and more affordable platform of the two) in an academic referral centre in South Africa by describing the dimensions and anatomical parameters of specimens resected and using this to investigate whether any of these are predictive of recurrence, and to evaluate the incidence of complications of this less radical technique.

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CHAPTER 2

2. Publication-ready Manuscript

(As per 2017 British Journal of Surgery Instruction to Authors)

2.1 Title Page

2.1.1. Title

Transanal Endoscopic Operation (TEO) – Local experience in a South African Setting

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2.2 Abstract

TITLE: **Transanal Endoscopic Operation (TEO) – Local experience in a South African Setting**

Background

It is well recognised that the adenoma-carcinoma sequence is the mechanism by which most colorectal malignancies arise. Dysplastic adenomas are the precursor lesions which can progress to adenocarcinoma and premalignant sessile villous adenomas represent a particular challenge. Their early detection and removal can prevent rectal cancer. Local excision of low rectal tumors has become increasingly popular as technical advancement has rendered it easier and more effective. Local tumour excision avoids the complications of radical surgery. Transanal endoscopic operation (TEO) and Transanal endoscopic microsurgery (TEM) are two equivalent techniques that have been widely adopted as the treatments of choice for large rectal adenomas and selected rectal cancers but has been under-employed in South Africa.

The aim of this study was to evaluate TEO (the simpler and more affordable platform of the two) by describing the dimensions and anatomical parameters of specimens resected and using this to investigate whether any of these are predictive of recurrence, and to evaluate the incidence of complications of this less radical technique.

Methods

In this single surgeon study, data was collected from pre-existing patient files (paper and electronic) during the first half of the time period and during the second half, was prospectively entered into a database. It includes all patients undergoing resection of benign and malignant rectal tumours by TEO at a private (Kingsbury Hospital) and public health institution (Groote Schuur Hospital) from January 2009 – May 2017. Electronic records, including operation notes, histology and radiology were reviewed.

Results

Data was collected from January 2009 to May 2017. There were 110 patients in this study of which 87 (79.1%) were benign. There were 11 (12%) recurrences in this group. In the malignant group, there were 5 (21%) recurrences. The median

tumour length was 4.5cm (IQR 2.5) and median tumour area was 16cm^2 (IQR 20.11).

For benign lesions, there was a significant difference in recurrence in patients presenting with incontinence (χ^2 8.21, *p*-value<0.01, OR 16.7 (1.37-202.7)), lesions with involved surgical margins (χ^2 6.29 *p*-value 0.01, OR 6.75 (95% CI 1.02 - 35.7)) and circumferential tumours (χ^2 6.31 *p*-value 0.04, 6.5 (1.17-36.3)). The multinomial logistic regression model in this series for benign lesions revealed that only incontinence and involved surgical margins were independent predictors of recurrence. Complications occurred in 21 (19.1%) patients. A multinomial regression model showed that circumferential lesions, length of the tumour, and malignancy were predictive of complications.

Conclusion

This study constitutes the only report of TEO or TEM from a low- or middle-income country (LMIC). Both the recurrence and complication rates are in keeping with international results demonstrating the potential for this procedure to be safe and feasible in this LMIC setting, which will reduce the need for expensive, highly morbid radical surgery for benign and malignant disease. The recommendation is for a wider introduction of TEO in South Africa and other LMIC countries with the provision of adequate training.

2.3 Text of Article

Introduction

Colorectal cancer is one of the leading causes of death in developed countries and found to be the third most common cancer in men and third most common cancer worldwide.[1–3]

It is well recognised that the adenoma-carcinoma sequence is the mechanism by which most colorectal malignancies arise.[4,5] Dysplastic adenomas are the precursor lesions which can progress to adenocarcinoma. Early detection and removal can prevent rectal cancer.[6]

Transanal endoscopic operation (TEO), which equates to the technique of Transanal microsurgery (TEM), has been widely adopted as the treatment of choice for large rectal adenomas, but has been little practised in South Africa with the exception of two centres in Cape Town, which attracted a large number of tertiary referral patients.

The excision of rectal lesions has evolved from invasive conventional rectal resection to include transanal excision, endoscopic mucosal resection, endoscopic submucosal dissection and in the last 30 years, TEM and TEO.[7]

The advantages of TEO over standard transanal excision include better exposure of the rectum, with lower recurrence and complication rates.[8]

There is no data regarding the South African experience of outcomes of TEO for benign rectal adenomas and early rectal cancer.

The aim of this study was to evaluate TEO (the simpler and more affordable platform of the two) by describing the dimensions and anatomical parameters of specimens resected and using this to investigate whether any of these are predictive of recurrence, and to evaluate the incidence of complications of this less radical technique.

Methods

Study Design

This is a mixed design study using both retrospective and prospectively collected data and evaluates the outcomes of a single surgeon case series from both a private and an academic hospital.

This research project includes patients who presented with benign and malignant rectal cancer at a private (Kingsbury Hospital) and public health institution (Groote Schuur Hospital) undergoing a Transanal Endoscopic Operation (TEO) from January 2009 to May 2017, comprising 110 patients.

Clinical records, including operation notes, histology and radiology were interrogated for these patients. The variables which were collected in the database include: symptoms, tumour length (defined as the largest diameter), tumour surface area, height of tumour, extent of circumferential involvement, histology (pre-operative and final), details of the procedure, length of stay, complications, recurrence and time to recurrence. Also assessed was the microscopic margin and surgeon assessed margin (endoscopic or surgical). Although margins were usually assessed endoscopically, lesions extending into the anal canal required an initial open approach to mobilise the lower anal margin. In this instance, the surgeon recorded the margin as a surgical margin. Data was collected retrospectively from 2009 to 2013 and prospectively from 2014 to May 2017.

Data collection

For the private sector patients, data was extracted from the online database, *Medscreen*, an in-house purpose designed practice database, on which each patient's notes, endoscopic photographs, radiology, histology and operative reports are recorded. Pathcare Laboratories performed the histological analysis. In the public sector, data was collected from patient folders, the operative reports from an electronic folder and histological results from the National Health Laboratory Service.

The size of the lesions was divided into small (less than 2cm), large (2 - 4cm) and giant, (4cm or greater). This classification was used in the absence of any uniform classification in the literature. It reflects a number of other articles citing these measurements.

Patient selection

All patients who underwent a TEO during the study period for both benign and malignant disease were included. All patients underwent colonoscopy and pre-operative biopsies prior to surgery. Many tertiary referral patients had these done prior to initial consultation. All patients underwent examination and at least a sigmoidoscopy by the surgeon (RJB) where the height of the lesion would be assessed. Biopsy was repeated as necessary.

Patients with a malignant biopsy result underwent staging pelvic MRI to evaluate their suitability for local excision. After its use early in the series, ERUS (endorectal ultrasound) was abandoned, as it was not found to be sufficiently accurate to facilitate decision-making.

Transanal Endoscopic Operation

All patients were prepared with a full bowel prep the previous evening. They were all consented for the possibility of intentional or inadvertent peritoneal entry, possibly requiring immediate corrective abdominal surgery, including the possibility of a stoma. Patients were not catheterised unless the procedure was unusually long or had been complicated. General anaesthesia was invariably used except where it was not considered safe by the anaesthetist, in which rare circumstance a spinal block was used. The patient was positioned in Lloyd-Davies. After a four quadrant anal block with bupivacaine infiltration, a slow and gradual anal stretch was undertaken, until the proctoscope could be passed without force. The lesion was resected usually using ultrasonic shears (Harmonic® Ultrasonic HD 1000i Shears, Ethicon Endosurgery) or sometimes monopolar diathermy. Defects were closed selectively using a V-Loc suture (V-Loc™ wound closure device, Medtronic/Covidien) after the tumour bed had been copiously irrigated.

Where the lesion extended into the anal canal, preventing an air seal at its lower margin, the procedure was initiated as an open dissection with anal retraction. Once sufficient sphincter had been cleared to allow a seal, the proctoscope was placed and the procedure completed endoscopically. Every effort was made to excise the lesion as a single intact specimen, but for very large carpet lesions it was sometimes necessary to do the resection piecemeal in order to maintain adequate visibility. Where necessary, the proximal mucosal margin was sutured to the anoderm to restore the muco-cutaneous bridge and avoid stricturing. Where the peritoneum was

breached, a full thickness closure was undertaken. After this, laparoscopy was sometimes performed to ensure complete closure and perform an air test to exclude a leak. All specimens were submitted pinned on a corkboard.

Statistical Analysis

Microsoft Excel 2017 (Redmond, Washington, USA) and Mathematica Version 11 (Champaign, Illinois, USA) were used for data collection and analysis.

Research variables were categorised as: nominal categorical, ordinal categorical and continuous numerical. The continuous numerical variables were analysed for the assumptions of the use of parametric tests by way of the Shapiro-Wilke test and quantile-quantile plots. The distribution of continuous numerical variables that failed these assumptions were analysed using non-parametric tests. The Student's *t*-test for independent groups, assuming equal variance was used as the parametric test and the Mann-Whitney-U test was the non-parametric test used. Point estimates and measures of dispersion for parametric tests were expressed as mean and standard deviation and for non-parametric tests were expressed as median and interquartile range, except for age, where dispersion was expressed as a range.

Proportions for categorical variables were examined using the chi-squared test for independence.

A multinomial regression model was created to predict recurrence.

An alpha value of 0.05 was used to indicate significance and a confidence level of 0.95 (95%) was used throughout.

Results

One-hundred and ten patients were included in the review of which were 57 male (51.8%). The median age was 67 years (range 24 – 92). Ninety-three (84.5%) patients were referred from elsewhere with a confirmed diagnosis. Thirty-four (30.9%) presented with rectal bleeding, 28 (25.4%) with a change in bowel habit and six (5.5%) with incontinence. At final histology there were 47 adenomas with low grade dysplasia (42.7%), 33 with high grade dysplasia (30%), 23 with adenocarcinoma (20.9%) and one traditional serrated adenoma (0.91%). The rest of the patients had a fibrous scar or no disease (6 patients, 5.45%). The adenocarcinomas were comprised of 14 T1 tumours (60.9%), seven T2 tumours (30.4%) and two T3 (8.69%). In total, there were 87 (79.1%) benign lesions and 23 (20.9%) malignant lesions. The median duration of follow-up was 15 months (0-91).

The tumour dimensions were evaluated in terms of length and area. The median tumour length was 4.5cm (IQR 2.5) and the median tumour area was 16cm^2 (IQR 20.11). The median length was 4.5cm (IQR 2.5) for benign lesions and 5cm (IQR 2.4cm) for malignant lesions. The median tumour area was 15.8cm^2 (IQR 19.6) for benign lesions and 18cm^2 (IQR 19.4) for malignant lesions. (Table 1)

Table 1: Length and Area for Benign and Malignant Specimens

	Benign (IQR)	**Malignant (IQR)**
Median Length	4.5cm (2.5)	5cm (2.4)
Median Area	15.8cm^2 (19.6)	18cm^2 (19.4)
Total	87	23

Length in cm and area in cm^2

The tumour involved less than half the circumference in 72 patients (65.5%), more than half the circumference in 31 patients (28.2%) and it was completely circumferential in 7 patients (6.36%). Size was also categorized into small, large and giant. (Table 2)

Table 2: Overall size and comparison of benign and malignant

	Benign	**Malignant**	**Total**
Small	2 (66.67%)	1 (33.3%)	3 (2.7%)
Large	27 (79.4%)	7 (20.6%)	34 (30.9%)
Giant	58 (79.5%)	15 (20.5%)	73 (66.3%)
Total	87	23	110

Size (cm)

Over 90% of patients with benign polyps had clear endoscopic or surgical margins. But there was microscopic involvement in 16 (18.4%). Similarly, with indeterminate lesions, there was a disparity between the margins assessed as being indeterminate by the surgeon (1.2%) and the pathologist (12.6%). (Table 3) There were similar proportions in the surgically involved margins between benign and malignant lesions (χ^2 1.98, *p*-value 0.37). There were also similar proportions in the microscopically involved margins between benign and malignant lesions (χ^2 0.35 *p*-value 0.84). (Table 3)

Table 3: Surgical and histological margins for benign and malignant lesions

Surgical Margins	**Benign**	**Malignant**
Clear (R0)	80 (91.9%)	23 (100%)
Involved (R1)	6 (6.9%)	0 (0%)
Indeterminate (Rx)	1 (1.2%)	0 (0%)
Microscopic Margins		
Clear (R0)	60 (69%)	16 (69.6%)
Involved (R1)	16 (18.4%)	5 (21.7%)
Indeterminate (Rx)	11 (12.6%)	2 (8.7%)

Height of the lower border of the tumour was measured in centimeters from the anorectal ring. While some of these lesions extended below the anorectal ring and were given a minus value, the median height was 3cm (IQR 5). There was no statistically significant difference in the height of the tumour in the 3 macroscopic margin groups (*p*-value 0.28). Similarly, in the 3 microscopic margin groups (*p*-value 0.12) there was no statistically significant difference.

Recurrence

The median time to recurrence was 14.3 months (IQR 28.9). Management of patients who developed a recurrence included: endoscopic excision (11), endoscopic ablation (1), repeat TEO (1), EMR (1), laparotomy (1) and no further intervention (1).

Benign Lesions

In the cohort of patients with benign lesions, 46 (52.9%) were male and 41 (47.1%) female. The median age was 64.8 years (range 35 - 92).

Of the 87 patients with benign lesions, 11 patients developed a recurrence (12.6%).

A number of variables were compared in patients who developed recurrence and those who did not. These variables were: gender, age, presenting symptoms (bleeding, change in bowel habit, incontinence), height, lesions more than a half of the circumference, circumferential lesions, size of tumour (in mm), piecemeal dissection, the involved surgical margins, involved histological margins and complications. A multinomial logistic regression model was constructed to predict recurrence using these variables.

There was a statistically significant recurrence rate among patients who presented with incontinence (χ^2 8.21, *p*-value<0.01), those with circumferential lesions (χ^2 6.44, *p*-value 0.04) and those in whom the surgical margins were involved (χ^2 6.4, *p*-value 0.04, odds ratio 5.19 (95% CI 1.04 – 25.9)) (Table 4)

Of these single variable logistic regression evaluations, the variables that had a p-value <0.2 were included: Bleeding, incontinence, Height, circumferential lesions, piecemeal, involved surgical margins and complications.

Only incontinence (*p*-value 0.01, OR 37.66 (CI 2.14 - 664)) and involved surgical margins (*p*-value 0.02, OR 12.9 (CI 1.47 -113) significantly increased the odds of recurrence. (Table 4)

Table 4: Single variable logistic regression to determine predictors of local recurrence for benign lesions

Variables	**Recurrence**	**No Recurrence**	**Chi^2, *p*-value**	**OR (95% CI)**
Gender			χ^2 1.48, *p*-value 0.24	0.46 (0.12-1.71)
M	34	42		
F	7	4		
Age	61.1 yrs (46-84)	65.4 yrs (35-92)	*p*-value 0.22	0.96 (0.91-1.03)
Symptoms				
Bleeding	5	17	χ^2 2.71, *p*-value 0.1	2.89 (0.78-10.65)
No bleeding	6	59		
Change in bowel habit	4	18	χ^2 0.82, *p*-value 0.37	1.84 (0.48-7.01)
No change in bowel habit	7	58		
Incontinence	2	1	**χ^2 8.21, *p*-value<0.01**	**16.7 (1.37-202.7)**
No incontinence	9	75		
Height	3 cm (IQR 5)	5.5 cm (IQR 6)	*p*-value 0.19	0.88 (0.72-1.07)
Circumference			**χ^2 6.31 *p*-value 0.04**	
Less than half	6	52		
More than half	2	40		0.87 (0.16-4.66)
Circumferential	3	4		**6.5 (1.17-36.3)**
Tumour length	34mm (IQR 16mm)	34mm (IQR20.8)	*p*-value 0.66	1 (0.98-1.04)
Piecemeal	3	8	χ^2 2.44 *p*-value 0.12	3.19 (0.87-14.5)
Not piecemeal	8	68		
Surgical Margins			**χ^2 6.29 *p*-value 0.01**	**6.75 (1.02-35.7**)
Clear	8	72		
Involved	3	4		
Histological Margins			χ^2 1.22 *p*-value 0.27	2.05 (0.57-7.4)
Clear	6	54		
Involved	5	22		
Complications	4	10	χ^2 3.83 *p*-value 0.05	3.77 (0.93 -15.2)
No complications	7	66		

OR – Odds Ratio, 95% CI – 95% Confidence interval (Single variable logistic regression)

Malignant Lesions

On final histology, only 23 lesions were malignant. Similar variables were used in the analysis. None of these could be shown to be predictors of recurrence. (Table 5)

Table 5: Single variable logistic regression to determine predictors of local recurrence for malignant lesions

	Recurrence	**No Recurrence**	**Chi^2, *p*-value**	**OR (95% CI)**
Gender M F	 1 4	 11 7	χ^2 2.65, *p*-value 0.1	6.29 (0.58-68.4)
Age	62.2yr (24-90)	69.7 (47-91)	*p*-value 0.35	0.97 (0.91-1.03)
Symptoms Bleeding No bleeding	 2 3	 10 8	χ^2 0.38, *p*-0.54 value	0.53 (0.07-4)
Change in bowel habit No change in bowel habit	2 3	4 14	χ^2 0.05, *p*-value 0.82	2.33 (0.28-19.2)
Incontinence No incontinence	1 4	2 16	χ^2 0.05, *p*-value <0.82	2 (0.14-28)
Height	3.8 cm (SD1.3)	4.22cm (3.19SD)	*p*-value 0.78	0.95 (0.66-1.36)
Circumference Less than half More than half Circumferential	 1 4 0	 13 5 0	χ^2 4.48 *p*-value 0.03	 10.4 (0.92-117)
Tumour length	27.4 mm (SD24)	26.7mm (SD 17)	*p*-value 0.97	1 (0.95-1.06)
Piecemeal Not piecemeal	1 4	0 18	χ^2 0.49 *p*-value 0.48	
Surgical Margins Clear Involved	 5 0	 18 0		
Histological Margins Clear Involved	 3 2	 13 5	χ^2 <0.01 *p*-value 0.98	1.7 (0.22-13.7)
Complications No complications	3 2	4 14	χ^2 1.16 *p*-value 0.28	5.25 (0.64 -43.1)

Complications

Eighty-nine (80.9%) patients did not have complications. Complications occurred in 21 (19.1%) patients and were distributed as follows: Five (4.5%) had a perforation (one of whom had an anterior resection and one had a Hartmann's), three had an immediate laparoscopy (all of whom had no defect noted after suture closing during TEO), six patients (2.7%) had asymptomatic mild anal or rectal strictures, three patients had post-operative bleeding (one of whom required an EUA and cautery and one of whom required an EUA and haemostatic rectal sponge and transfusion), three (2.7%) had urinary retention and one patient developed a rectovaginal fistula which required a defunctioning stoma until spontaneous healing whereupon the stoma was closed uneventfully. One patient reacted adversely to anaesthesia, with a mild cholinergic syndrome which resolved promptly (0.91%), one had mild faecal incontinence which resolved within 3 months (0.91%) and two patients required re-look laparotomies.

There was no significant difference between the proportions of complications between patients with benign and malignant polyps (χ^2 2.42, *p*-value 0.12). (Table 6)

Table 6: Summation of complications for benign and malignant polyps

	Complications	**No complications**
Benign	14 (16.1%)	73 (83.9%)
Malignant	7 (30.4%)	16 (69.6%)

Patients with complications had a median carpet length of 5.5cm (IQR 2.5) compared to those without complications who had a median length of 4.4cm (IQR 2.1) (*p*-value 0.01). There was no difference in complications between those with small, large and giant lesions (χ^2 4.49 *p*-value 0.11). There was a significant difference between tumour circumference and complications (χ^2 23.3, *p*-value < 0.01). (Table 7)

Table 7: Complications in relation to size and circumferential involvement

	Complications (%)	**No complications (%)**	**Total**
Small	0 (0.0%)	3 (100%)	3
Large	3 (8.8%)	31 (91.2%)	34
Giant	18 (32.7%)	55 (75.3%)	73
Less than half	8 (11.1%)	64 (88.9%)	72
More than half	7 (22.6%)	24 (77.4%)	31
Circumferential	6 (85.7%)	1 (14.3%)	7

The median height of the lesions in patients who had a complication and in those with no complications was both 3 cm (IQR 7).

A multinomial logistic regression model was constructed to predict complications. The predictive variables chosen for assessing complications were: Lesions more than half the circumference, circumferential lesions, piecemeal dissection, involved endoscopic or surgical margins, involved microscopic margins, tumour length, width, height and the presence of a malignancy.

The presence of a circumferential lesion significantly increased the odds of a complication compared to a lesion that was less than a half of the circumference (*p*-value <0.01, OR 1.07 (CI 3.2 - 1196)). Length (*p*-value 0.04, OR 1.06 (CI 1 – 1.12) and malignancy (*p*-value < 0.01, OR 5.8 (CI 1.55 – 22.4) were similarly a predictive of the development of a complication

Correlation of biopsy with final histology

A comparison between the histology of the pre-operative biopsy and the post-operative specimen revealed that the histology was the same in only 60 patients (54.5%). This results in a sensitivity of 41%, a specificity of 93.2%, a positive predictive value of 60% and a negative predictive value of 86.3%. (Table 8)

Table 8: The Comparison of Pre-operative and Final Histology

		Final Histology	
		Benign	**Malignant**
Pre-operative biopsy	**Benign**	82	13
	Malignant	6	9

Mortality

Ten (9.1%) patients in this series died but their deaths were unrelated to the procedure or diagnosis.

Discussion

Historically, the indications for TEO and TEM included benign polyps and invasive lesions in patients who were evaluated as being unsuitable for radical resection. With increasing experience, circumferential and more proximal polyps are now managed with TEO. There are now reports of TEO being used in the management of fistulous disease (high anorectal fistulas, rectourethral & rectovaginal fistulas). Other more exotic indications in high volume centres included GISTs, anastomotic strictures, correction of rectal prolapse and most pertinently, early stage rectal cancer.[9–11]

The aim of this study was to evaluate TEO (the simpler and more affordable platform of the two) by describing the dimensions and anatomical parameters of specimens resected and using this to investigate whether any of these are predictive of recurrence, and to evaluate the incidence of complications of this less radical technique.

Nearly 80% of specimens were benign but a comparison between the histology of the pre-operative biopsy and the final histology revealed very poor correlation with a negative predictive value of 86.3%. This is most likely due to sampling error, because a small malignant focus was often found within the much larger villous carpet, so that the pre-operative biopsies of the carpet could easily miss the cancerous component. In this study, there were unexpected malignancies in 13.68% of lesions. This is remarkably consistent with the findings in the 2017 TREND study, the first randomised controlled trial comparing the clinical outcomes and cost effectiveness of TEM and EMR for large rectal adenomas.[12]

Nearly 15% of patients developed recurrence. The 12.6% recurrence rate in the benign polyp cohort is consistent with other series where recurrence rates ranged from 5.1 – 15.8%.[10,13–17] In this series, incontinence as a presenting symptom, circumferential lesions and involved surgical margins were significant in patients who developed recurrence. While height was not significant, patients with lower lesions extending to the anal canal had a higher incidence of recurrence. The failure to achieve significance is likely a type II error, that is, failure to detect an effect that is present, usually resulting from insufficient sample size. These recurrences are likely to result from the closer distal margins in these anal canal lesions used to prevent damage to the anal sphincters. The border of these tumours would commonly be

involved or within 1mm of the cauterised margin. This diathermy artefact could explain the discrepancy between the surgeon recording a clear margin and the pathologist reporting it as involved or indeterminate.

A multinomial analysis of the risk of recurrence in a retrospective study aiming to identify predictor variables for recurrence after TEM found that only involved microscopic margins were significant.[17] The multinomial logistic regression model in this series for benign lesions revealed that only incontinence and involved surgical margins were significant predictors of recurrence. The correlation with recurrence must be explained by the size and distal location of the lesion. Larger lower lesions are most likely to produce larger volumes of mucus close to the sphincter, thus causing a mucous leak. These large low lesions are sometimes chronically prolapsed, also rendering the patient wet and complaining of incontinence.

Hypotheses for recurrence include incomplete removal of the lesion and the concept of instability of the rectal mucosa and field changes, where a tendency to dysplasia and villous formation in the adjacent rectal mucosa remains despite the lesion being excised. This was supported in several cases where polyp 'recurrence' was situated several centimetres from the tumour scar. Another explanation might be exfoliation and re-implantation of viable tumour cells.[18–20]

A positive margin is a strong predictor of recurrence, and large adenomas have a higher rate of recurrence.[17] In this study, over 90% of patients with benign polyps had clear endoscopic or surgical margins. However, of these, there was microscopic involvement in 18.4%. Similarly, in lesions with indeterminate margins, there was a disparity between the margins assessed as being indeterminate by the surgeon (1.2%) and the pathologist (12.6%). This disparity was most often seen in the larger lesion and circumferential lesions which may have been removed piecemeal. While enormous care was taken by the surgeon to pin all completely excised specimens to a corkboard in an attempt to preserve the margin between normal tissue and tumour, specimen handling remains a possible contributory factor.

In the benign cohort, 31% were large lesions (2 - 4cm) and 67% were giant lesions (> 4cm). While this is comparable with the international literature where the median sizes ranged from 3–5.7cm,[10,13–16] it reflects severe under-reporting of the size as the measurements were taken after being placed in formalin which causes shrinkage.

One study, describing giant circumferential adenomas, had a median size of 7cm (3-10 cm) and a recurrence rate of 23.5%.[11]

Complications, in this series, occurred in 21 (19.1%) patients and are comparable with the literature where the complication rate ranged from 0% to 35.7%.[10,11,13–15,21–24] Lesion size and circumferential involvement were statistically significant when comparing patients who developed complications to those who did not. However, serious complications requiring laparoscopy and stoma formation correlated with higher lesions, especially when situated anteriorly. A multinomial regression model demonstrated that the presence of a circumferential lesion, the length of the lesion and malignancy were predictive of a complication.

Limitations

There are a number of limitations in this study which should be addressed in future research. While this is a substantial series of TEO procedures, nevertheless the patient numbers are insufficient to determine significant outcomes. Another limitation was the possible under-reporting of the size of the lesions. The specimen measurements were taken after fixation with formalin that causes shrinkage of tissue.

Conclusion

This study constitutes the only report of TEO or TEM from a low- or middle-income country (LMIC). Both the recurrence and complication rates are in keeping with international results demonstrating the potential for this procedure to be safe and feasible in this LMIC setting, which will reduce the need for expensive, highly morbid radical surgery for benign and malignant disease. The recommendation is for a wider introduction of TEO in South Africa and other LMIC countries with the provision of adequate training.

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CHAPTER 3

3. Appendices

3.1 Departmental Approval Document

UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee
Professor Anwar Suleman Mall
J-45 Room Old Main Building, Groote Schuur Hospital,
Observatory 7925, South Africa
Tel (021) 406 6168/6232/6227 Fax (021) 448 6461
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22nd July 2014

Dr P Karjiker
Department o f Surgery
Division of General Surgery
University of Cape Town

Dear Dr Karjiker,

RE: PROJECT 2014/066

PROJECT TITLE: TEO- A review of cases in a Southern African setting

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

3.2 Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.arieffdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

04 May 2015

HREC/REF: 265/2015

Prof R Baigrie
General Surgery
J-45.69
OMB

Dear Prof Baigrie

Project Title: TRANSANAL ENDOSCOPIC OPERATION (TEO) - LOCAL EXPERIENCE IN A SOUTH AFRICAN SETTING (MMeD-candidate-Dr P Karjiker)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 28 May 2016.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:- Dr Parveen Karjiker is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:265/2015

UNIVERSITY OF CAPE TOWN
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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/05/18
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	29/5/2017

HUMAN RESEARCH ETHICS COMMITTEE
29 MAY 2017
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	26 MAY 2017		
HREC REF Number	266/2015	Current Ethics Approval was granted until	~~26 MAY 2016~~
Protocol title	TRANSANAL ENDOSCOPIC OPERATION (TEO) – LOCAL EXPERIENCE IN A SOUTH AFRICAN SETTING		
Principal Investigator	DR PARVEEN KARJIKER		
Department / Office Internal Mail Address	DEPARTMENT OF GENERAL SURGERY PARVEEN.KARJIKER@GMAIL.COM		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		110
Total number of records or specimens collected, reviewed or stored since last progress report		110
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☑ Yes	☐ No

4. Signature

Signature of PI	P. KARJIKER	Date	26/05/2017

3.3 British Journal of Surgery Instructions to Authors

2017 BJS Instructions to Authors

BJS publishes original articles, reviews, meta-analyses, systematic reviews and randomized clinical trials, all of which are submitted to rigorous peer review. BJS subscribes to the policies published by the International Committee of Medical Journal Editors (ICMJE)[1] and adheres to publishing ethics guidelines published by the Committee on Publication Ethics (COPE)[2].

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Before acceptance there is no requirement to inform the Editorial Office that you intend to publish your paper OnlineOpen if you do not wish to. All OnlineOpen articles are treated in the same way as any other article. They go through the journal's standard peer-review process and will be accepted or rejected based on their own merit.

Guidelines publication

The BJS editorial team welcomes proposals that might lead to the publication of evidence-based guidelines relevant to surgical practice, acknowledging that the best available evidence might be no more than a consensus view. Potential authors are encouraged to submit initial ideas for consideration, and not completed documents, to assess whether publication in BJS is possible.

Before guidelines are submitted, an outline proposal not exceeding 500 words should describe:

– The intended guideline topic. This can include any issue directly relevant to clinical surgery, but should explain the need for guidelines on the chosen topic.
– The proposed methodology. This might include the use of systematic reviews, a Delphi consensus or combinations of methodologies, but should be specified, along with an estimate of the life span of the guidelines.
– Details of the group responsible for the guidelines. This should indicate the involvement of professional associations or societies, and commercial organisations. Sponsorship or funding details should be provided in this section. The tasks and contributions to be undertaken by each author should be listed.
– Geographic origin and extent of influence. The relevance of the guidelines and their influence should be explained in global terms. Guidelines that relate to the healthcare systems of a single country are unlikely to be accepted.

Proposals considered suitable by the editors will be sent for peer review. As with all other submissions to BJS, acceptance is likely to be conditional, subject to editorial and reviewers' comments. A designated BJS Editor will work with the responsible group to ensure consistency of style and prompt publication.

The outline proposal should be submitted online through ScholarOne Manuscripts (details below). Please note that there are many mandatory sections during submission that are not relevant to Guidelines. Please mark these as 'N/A' in the ScholarOne submission.

1. Important information for authors

An article is reviewed for publication on the assumption that its contents have not been submitted simultaneously to another journal, have not been accepted for publication elsewhere and have not already been published[3]. Authors will be asked to confirm that this is the case during the electronic submission process. Any attempt at dual publication will lead to automatic rejection, may prejudice acceptance of future submissions, and may be highlighted within the pages of the Journal. Please submit with your manuscript copies of any other papers (including abstracts) – published, in press, or submitted for consideration elsewhere – that relate in whole or in part to the same data set; this is essential to enable assessment of any potential overlap by the Editors. Indicate on the title page whether the paper is based on a previous communication to a society or meeting.

Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

2. Article types

Please note that BJS does not publish case studies.

a) Leading articles

The Editors commission leading articles of 800–1000 words and up to ten references. A single author is preferred. Submissions may be subjected to peer review and the Editors retain the right to alter textual style.

b) Reviews (including systematic reviews and meta-analyses)

Priority will be given to work that addresses a topic of current interest. All meta-analyses of randomized trials must adhere to the guidelines outlined in the PRISMA statement, which is designed to improve manuscript quality[4]. It is strongly recommended that the PRISMA statement is used in conjunction with the PRISMA Explanation and Elaboration Document[5] and PRISMA abstracts guidelines[6]. The PRISMA for abstracts checklist gives authors a framework for condensing their systematic review and meta-analysis into the essentials for an abstract.

Authors must include a suitable PRISMA flow chart in their submission. The flow diagram depicts the flow of information through the different phases of a systematic review. A template of the PRISMA flow diagram is available here as a Word document.

Other useful resources for authors of review articles include the article Systematic reviews and meta-analysis for the surgeon scientist by Galandiuk and colleagues[7], and the Cochrane Handbook for Systematic Reviews of Interventions[8].

BJS will consider for publication Cochrane review articles that have been substantially shortened and re-written for a surgical audience. Such submissions must state this on the title page of the manuscript, and copies of the original article must be

sent to the Editorial Office for consideration. You must be the author of the Cochrane review and must also apply for permission from the Cochrane Library – further information on how to do this is available in the Cochrane Manual9. These articles will be subject to the usual BJS peer-review process and will usually be published only if submitted within 6 months of publication of the Cochrane Review.

c) Prospective clinical trials

BJS expects all authors to register prospective clinical trials in a suitable electronic and freely accessible registry (e.g. www.clinicaltrials.gov, www.controlled-trials.com), according to the ICMJE guidelines[1,10]. For this purpose, a clinical trial is defined as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between an intervention and a health outcome. The registration number of the clinical trial should be quoted at the end of the abstract. If you wish the Editor to consider an unregistered trial, please explain why the trial has not been registered.

In addition, all randomized clinical trials must adhere to the guidelines outlined in the CONSORT statement[11,12]. It is strongly recommended that the CONSORT statement is used in conjunction with the CONSORT Explanation and Elaboration Document[13]. Investigators must include a suitable CONSORT flow chart in their submission. The CONSORT 2010 Flow Diagram template can be downloaded here. Furthermore, it is strongly advised that the CONSORT for abstracts guidelines are consulted[14].

The primary end point of the trial and the power calculation must be stated clearly stated. Randomized clinical trials should be identified as such in both the title and the abstract.

The main CONSORT Statement is based on the 'standard' two-group parallel design. However, there are several different types of randomized trials with other designs. To help improve the reporting of these trials the CONSORT group has extended and modified the main CONSORT Statement for application in various areas, and the resulting CONSORT extensions can be found on http://www.consort-statement.org/extensions[12].

d) Original articles

Original articles should normally be in the format of Introduction, Methods, Results and Discussion. A structured abstract of fewer than 250 words should be provided (further details on this can be found below).

e) Observational studies

STROBE is an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal Editors involved in the conduct and dissemination of observational studies, with the common aim of STrengthening the Reporting of OBservational studies in Epidemiology[15]. STROBE makes recommendations to the three main analytical designs that are used in observational research: cohort, case-control, and cross-sectional studies. Please visit to STROBE website for more information and available checklists (http://www.strobe-statement.org/).

f) Experimental papers

Papers involving experimental or animal research are sometimes challenging to read. The Editors wish to encourage authors to submit high-quality experimental research for publication in BJS, particularly if it has obvious clinical or translational relevance. To try and improve the quality of experimental research published in BJS, future submissions will generally be restricted to a maximum of 3500 words, a combined

total of five figures and tables, and 30 references. Additional material over and above these instructions could be published as supplementary material online.
Authors should also submit a 150-word summary describing the surgical relevance of the paper, which will be published on the front page together with the abstract. The aim is to provide a short section of text explaining the potential clinical relevance of the study using the following structure: what is already known, what is new, and the potential impact on future practice. One or two short sentences under each heading will suffice.

Authors of papers involving animal research must follow the ARRIVE Guidelines (Animal Research: Reporting *In Vivo* Experiments)[18]. Please follow this link for details[19].
The **equator network** website offers more information on enhancing the quality, transparency of reporting health care studies including key reporting guidelines. Please have a look at http://www.equator-network.org.

g) Snapshots in Surgery
BJS publishes illustrations in the print issue that are used as the basis for a surgical quiz. We consider single surgical images in colour that are of educational value to surgeons.
Specifications:
All illustrations must be in colour and of a high quality (>400dpi, preferably TIFF or EPS files); they must not have been published previously. Snapshots should be accompanied by a short question that might be general (e.g. what is this condition, and how should it be treated?), or multiple choice. The authors must also provide the answers to the quiz using text of no more than 100 words. Images of patients should be accompanied by a signed consent form available here.
Snapshots in Surgery should be submitted online at http://mc.manuscriptcentral.com/bjs. Please note that there are many mandatory sections during submission that are not relevant to Snapshots in Surgery. Please mark these as 'N/A' in the ScholarOne submission.
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h) Your comments
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3. Preparation of manuscripts

BJS subscribes to the policy of uniform requirements for manuscripts; this facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the Uniform Requirements for Manuscripts Submitted to Biomedical Journals[1]. BJS accepts the criteria for authorship proposed in the ICMJE[1,11] and subscribes to the COPE guidelines on good publication practice[2]. These guidelines are summarized below.

a) Authorship

BJS seeks to minimize the risk of gratuitous authorship by limiting the number of authors listed in an article. BJS holds the view that in the context of surgical publishing, most articles are unlikely to involve significant contributions from more than ten authors. For our full authorship policy and information on how multiple authorship should be handled please click http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

For articles with more than ten authors, BJS requests that this form be completed and submitted alongside the manuscript. Please ensure that all conditions listed in the form are met and that all authors sign it.

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The corresponding author is responsible for ensuring that all authors have seen, approved and are fully conversant with the contents of the manuscript. All authors are responsible for the accuracy of the manuscript, including all statistical calculations and drug doses.

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4. Submission guidelines

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b) Title page
On the title page please state: (1) the title of the article; (2) the name and initials of each author; (3) the department(s) and institution(s) to which the work should be attributed; (4) the name, postal and e-mail addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of funding for research and/or publication; (6) the category in which the manuscript is being submitted (original article, review, randomized clinical trial); and (7) whether the paper is based on a previous communication to a society or meeting (with full details).

c) Abstract
This must contain fewer than 250 words in a structured format. Background: state why the study was done, the main aim and the nature of the study (randomized clinical trial, retrospective review, experimental study, etc.). Method: describe patients, laboratory material and other methods used. Results: state the main findings, including important numerical values. Conclusion: state the main conclusions, highlighting controversial or unexpected observations. For systematic reviews/meta-analysis and randomized controlled trials please see guidelines for abstracts as reported by PRISMA and CONSORT[6,14].

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